Notice of Allowability	Application No.	Applicant(s)	
	09/938,112	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/21/05*.

2. ☒ The allowed claim(s) is/are *36,37,67,68,72-75,81 and 82*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Status of the Claims

1. Claims 21, 22, 36, 37, 67-75, 77 and 78 are pending.

Applicant's amendment filed February 21, 2005 is acknowledged, and applicants' response has been fully considered. Claims 21 and 69 have been amended. Therefore, claims 21, 22, 36, 37, 67-75, 77 and 78 are examined.

Withdrawn Claim Rejections - 35 USC § 101

2. The previous rejection of claims 21 and 22 under 35 U.S.C. 101, is withdrawn in view of applicant's amendment to the claim, and applicant's response at pages 7-8 in the amendment filed February 21, 2005.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 21 and 22 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at pages 7-8 in the amendment filed February 21, 2005.

4. The previous rejection of claims 69, 70, 71 and 73-75 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at pages 8-9 in the amendment filed February 21, 2005.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Greg Hollrigel on October 25, 2005.

Examiner's Amendment to the Specification:

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-amide" at page 26, Table 1, item (1) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-amide (SEQ ID NO:1)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly" at page 26, Table 1, item (2) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly (SEQ ID NO:2)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys" at page 26, Table 1, item (3) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys (SEQ ID NO:3)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg" at page 26, Table 1, item (4) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg (SEQ ID NO:4)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-OMe" at page 26, Table 1, item (5) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-OMe (SEQ ID NO:5)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-OMe" at page 26, Table 1, item (6) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-OMe (SEQ ID NO:6)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg-OMe" at page 26, Table 1, item (7) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg-OMe (SEQ ID NO:7)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-OEth" at page 26, Table 1, item (8) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-OEth (SEQ ID NO:8)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-OEth" at page 26, Table 1, item (9) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-OEth (SEQ ID NO:9)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg-OEth" at page 26, Table 1, item (10) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-Gly-Lys-Arg-OEth (SEQ ID NO:10)"

-Please replace the term "Arg-Pro-Lys-Pro" at page 27, Table 1, item (11) with the term "Arg-Pro-Lys-Pro (SEQ ID NO:11)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe" at page 27, Table 1, item (12) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe (SEQ ID NO:12)"

-Please replace the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly" at page 27, Table 1, item (13) with the term "Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly (SEQ ID NO:13)"

-Please replace the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Phe-Phe-Trp-Leu-Met-amide" at page 27, Table 1, item (14) with the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Phe-Phe-D-Trp-Leu-Met-amide (SEQ ID NO:14)"

-Please replace the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Phe-Phe-Trp-Leu-Met-Gly" at page 27, Table 1, item (15) with the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Phe-Phe-D-Trp-Leu-Met-Gly (SEQ ID NO:15)"

-Please replace the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-Trp-Leu-Met-amide" at page 27, Table 1, item (16) with the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trp-Leu-Met-amide (SEQ ID NO:16)"

-Please replace the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-Trp-Leu-Met-Gly" at page 27, Table 1, item (17) with the term "Arg-D-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trp-Leu-Met-Gly (SEQ ID NO:17)"

-Please replace the term "Arg-Pro-Cys-Pro-Gln-Cys-Phe-Tyr-Gly-Met-amide" at page 27, Table 1, item (18) with the term "Arg-Pro-Cys-Pro-Gln-Cys-Phe-Tyr-Gly-Pro-Met-amide (SEQ ID NO:18)"

Examiner's Amendment to the claims:

Cancel claims 21-22, 69-71, 77 and 78.

Claims 36, 37, 67, 68 and 73-75 have been amended, and new claims 81-82 have been added as follows:

36. (Currently amended) A plasmid encoding a modified clostridial neurotoxin, comprising:

(a) a first nucleotide sequence comprising~~;~~: (i) a first nucleotide segment encoding an amino acid sequence comprising ~~a targeting moiety of~~ substance P as the targeting moiety ~~able to specifically bind to receptors on cells under physiological conditions~~; and (ii) a second nucleotide segment encoding an amino acid sequence comprising a translocation ~~element able to facilitate the transfer of a polypeptide~~ domain (H_N) of a clostridial neurotoxin or a fragment thereof, which fragment translocates a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin across an endosome membrane,

wherein the first and second nucleotide segments encode an amino acid sequence comprising a fusion protein of a translocation domain and substance P, and wherein the H_C has been removed from said clostridial neurotoxin or has been modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction; ~~and~~

(b) a second nucleotide sequence encoding an amino acid sequence comprising ~~a therapeutic element having an intracellular protease biological activity when released into the cytoplasm or a target cell~~ the L-chain or an L-chain fragment of a clostridial neurotoxin, which L-chain fragment comprises the active protease domain of L-chain; and

(c) an element for ~~replication directing~~ plasmid replication by a host cell~~, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction~~.

37. (Currently amended) A method of making a modified clostridial neurotoxin, the method comprising:

(a) inserting the plasmid of claim 36 into a suitable host cell,

(b) culturing the host cell under conditions sufficient to express the clostridial neurotoxin, and

(c) isolating the clostridial neurotoxin.

67. (Currently amended) A method of obtaining an agent for alleviating pain, the method comprising:

(a) producing ~~a genetic construct having nucleic acids encoding~~ the plasmid of claim 36 which encodes a modified clostridial neurotoxin;

(b) ~~incorporating the construct~~ inserting the plasmid into a suitable host cell;

(c) culturing the host cell under conditions sufficient ~~for expression of~~ to express the clostridial neurotoxin; and

(d) ~~covalently attaching the expressed clostridial neurotoxin to substance P, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction~~ isolating the clostridial neurotoxin as the agent for alleviating pain.

68. (Currently amended) The method of claim 67, wherein the modified clostridial neurotoxin further ~~comprising covalently attaching~~ comprises at least one spacer component ~~between the clostridial neurotoxin and the substance P~~.

73. (Currently amended) The method of claim 72, wherein the H_N ~~is a translocation domain of a clostridial neurotoxin having~~ has an amino acid sequence ~~substantially~~ identical to the translocation domain of a clostridial neurotoxin from an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

74. (Currently amended) The method of claim 72, wherein the L-chain ~~is a light chain of a clostridial neurotoxin having~~ has an amino acid sequence ~~substantially~~ identical to the light chain of a clostridial neurotoxin from an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

75. (Currently amended) The method of claim 72, wherein the H_N ~~is a translocation domain of a clostridial neurotoxin having~~ has an amino acid sequence ~~substantially~~ identical to a the translocation domain of a botulinum toxin selected from the group consisting of botulinum toxin serotype A, serotype B, serotype C1, serotype D, serctype E, serotype F, and serotype G.

81. (New) The method of claim 72, wherein the H_N has an amino acid sequence identical to the translocation domain of a botulinum toxin selected from the group consisting of botulinum toxin serotype A, serotype B, serotype C1, serotype D, serctype E, serotype F, and serotype G, and wherein the L-chain has an amino acid sequence identical to the light chain of a botulinum toxin selected from the group consisting of botulinum toxin serotype A, serotype B, serotype C1, serotype D, serctype E, serotype F, and serotype G.

82. (New) The method of claim 72, wherein the H_N has an amino acid sequence identical to the translocation domain of botulinum toxin serotype A, and wherein L-chain has an amino acid sequence identical to the light chain of botulinum toxin serotype A.

The following is an **Examiner's Statement of Reasons for Allowance**: The following reference appears to be the closest art to the claimed invention. Quinn *et al.* (USPN 6,632,440) teach a compound which inhibits mucus secretion by mucus secretion cells, the compound comprising a light chain (L-chain) or a L-chain fragment of a clostridial neurotoxin, which L-chain fragment comprises the active protease domain of the L-chain, a targeting domain such as substance P, and a translocating domain of a clostridial neurotoxin that translocates the L-chain or L-chain fragment into the target cell; and a method of manufacturing the compound by recombinantly expressing a fusion protein of LH_N with the targeting domain. However, the reference does not teach or suggest a plasmid encoding a modified clostridial neurotoxin, comprising a first nucleotide sequence encoding a fusion protein of a translocation domain of a clostridial and substance P, a second nucleotide sequence encoding an L-chain, and an element for plasmid replication by a host cell; and a method of making the modified clostridial neurotoxin by expression in a host cell using the plasmid. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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October 25, 2005

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